

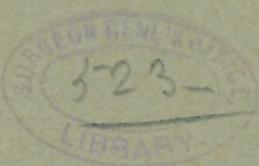
Billings (J. S.) Jr.

THERAPEUTIC USE OF EXTRACT OF BONE MARROW.

BY JOHN S. BILLINGS, JR.,

ASSISTANT RESIDENT PHYSICIAN, JOHNS HOPKINS HOSPITAL.

(Read before the Johns Hopkins Hospital Medical Society, November 5, 1894.)



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The use of bone marrow in cases of anæmia and in certain diseases of the blood-making organs was probably suggested by the success of the treatment of myxœdema with thyroid extract. The marrow is thought by most authorities to be the principal seat of formation of the red blood corpuscles. A diminution in number of the red corpuscles may be due to increased destruction or to diminished formation, and it was hoped that in either case the administration of the marrow as a medicine would stimulate the blood-making organs to increased activity, and thus make up the loss in red corpuscles.

The first case of anæmia treated in this manner was reported by Fraser.¹ A diagnosis of pernicious anæmia was made, based upon the history of the case, the number of red corpuscles and per cent. of haemoglobin, and the poikilocytosis of the red corpuscles. No mention was made as to the occurrence of nucleated red corpuscles, the presence of which in the blood in pernicious anæmia being a point upon which Ehrlich lays considerable stress. The case was given bone marrow with arsenic for the first two months, then bone marrow alone for a month, and finally bone marrow and iron for three months. In the first two months the corpuscles rose from 1,000,000 per cmm. to 4,000,000, ranging at the latter point until discharge, four months later.

Bigger² reports a case of leucocythaemia in a boy, which was treated with the bone marrow. There was rapid diminution in the size of the spleen and marked improvement within

¹ Brit. Med. Jour., June 2, 1894.

² Lancet, September 22, 1894.



a week. No mention is made of any examination of the blood, and it is possible that the case may have been one of splenic anaemia or of the pseudoleukæmic infantile anaemia of Von Jaksch.

Danforth¹ reports a case of pernicious anaemia apparently cured by the use of bone marrow. Here also the report of the blood condition is incomplete, as only the number of red corpuscles and per cent. of haemoglobin are stated. The latter rose from 35 per cent. to 80 per cent. The bone marrow in this case, as in that of Fraser, was given in combination with arsenic.

In our own cases the marrow was given in the form of a glycerin extract which was prepared in the following manner. Twelve sheep's ribs, carefully scraped, were chopped into small fragments and rubbed up in a mortar with one pound of glycerin. This was allowed to macerate for three or four days, being kept in a refrigerator during that time. It was then strained through gauze, and the resultant liquid administered in teaspoonful doses three times a day. No complaint was made by the patients with regard to its taste.

Case 1.—Chlorosis. Girl, aged 20; admitted June 21, 1894, complaining of dyspnoea and weakness. Past history was negative. Present illness of four months' duration. Physical examination showed nothing beyond marked anaemia, and a loud functional murmur along the left sternal margin.

Blood count on admission, reds 2,898,000, whites 5000; haemoglobin 32 per cent. Stained specimens of the blood showed nothing beyond the pallor of the centre of the red corpuscles, so characteristic of chlorosis. No treatment was instituted for the first ten days, *i. e.* until July 1st, when the extract of bone marrow was begun. The blood count at that time was, reds 3,198,000, whites 5500; haemoglobin 38 per cent. The extract was discontinued July 16, as patient insisted on leaving the hospital. The blood count on the morning of discharge was, reds 4,192,000, white 7000; haemoglobin 40 per cent. She was given Blaud's pills, and subsequently did well.

Case 2.—Chloro-anaemia in a boy. Past history was negative. For a month had complained of headache and gradually increasing weakness. Inspection showed a moderate grade of anaemia, physical examination being otherwise negative. On admission the

¹ Chicago Clin. Review, IV, 1894.

blood count was, reds 3,290,000 per cmm.; haemoglobin 35 per cent. Stained specimens of the blood showed nothing beyond the pallor of the centre of the red corpuscles. Such a blood condition in a young female would certainly lead to a diagnosis of chlorosis, but the diagnosis of chlorosis in the male is always hazardous. The extract of marrow was ordered, and the condition of the blood gradually improved, the red corpuscles reaching a normal point (5,000,000 per cmm.) in about a month. The haemoglobin rose more slowly, and on discharge (see chart 3) was only 68 per cent. As a rule, in chlorosis we must be satisfied if we can get the haemoglobin as high as 75 to 80 per cent.

Case 3.—Pernicious anaemia. Man, aged 51, admitted June 15, 1894, complaining of vomiting and progressive weakness. He was very pale, and had first noticed the pallor ten weeks before. Had not lost very much in weight. Inspection showed a marked grade of anaemia, with the lemon-yellow discolorization of the skin so frequently seen in pernicious anaemia. Physical examination and examination of the stomach contents were negative. The case was at first suspected to be one of cancer of the stomach, but the absence of tumor, the readiness with which the gastric symptoms yielded to treatment, and finally the condition of the blood, all pointed to its being a case of the idiopathic anaemia of Addison, the so-called primary pernicious anaemia. Blood count on admission, reds 1,148,000, whites 4400; haemoglobin 27 per cent. By July 1st the red corpuscles had sunk to 918,000, and the haemoglobin to 17 per cent. Stained specimens showed marked poikilocytosis and polychromatophilic staining of the red corpuscles. Several nucleated red corpuscles seen, the greater number being normoblasts. The remainder were typical megaloblasts, with large pale nuclei and polychromatophilic protoplasm. Many micro- and megalocytes. A differential count of the leucocytes showed the per cent. of the small mononuclear forms or lymphocytes to be increased to 34 per cent., almost twice the normal. This technical description of the blood condition is given to show the grounds on which the diagnosis was based. The absence of any apparent causative factor, and the fact that the per cent. of haemoglobin was relatively higher than that of the red corpuscles, confirmed the diagnosis. The use of the extract of bone marrow was begun June 30th. At first the blood condition improved, the red corpuscles rising to 1,400,000. They fell again to 970,000, however, and the extract was discontinued July 18th, it having been given 19 days without causing improvement. Fowler's solution was ordered in increasing doses, and the patient gradually improved, being discharged October 12th in fairly good condition. Blood count on discharge, reds 3,600,000, whites 7000; haemoglobin 69 per cent. Stained specimens showed no poikilocytosis, no nucleated red corpuscles, and the per cent. of the various forms of leucocytes was normal. (See chart 1.)

Case 4.—Pernicious anaemia. Man, aged 65, admitted August 15, 1894, complaining of weakness and shortness of breath. Illness began about one year before admission, and has been gradually progressing ever since. Has lost very little weight. Physical examination negative beyond a marked grade of anaemia. Skin distinctly lemon-tinged. The urine was high-colored, but of low specific gravity, a condition which has been frequently observed in pernicious anaemia, and which is supposed by Hunter to be due to the presence of pathological urobilin in the urine. The recent investigations of Hopkins (Guy's Hosp. Rep., 1893) would seem to make the existence of this substance improbable. He found only normal urobilin and haematoxophyrin in the urine in pernicious anaemia. Blood count August 18, reds 2,048,000, whites 5000; haemoglobin 45 per cent. Stained specimens showed a moderate grade of poikilocytosis, such as is seen in severe secondary anaemia. No nucleated red corpuscles. Percentages of leucocytes normal. The number of red corpuscles gradually sank, and between September 8th and October 6th ranged between 1,120,000 and 1,392,000; during this time patient was taking Fowler's solution.

Stained specimens of the blood taken September 2d showed marked poikilocytosis, many micro- and megalocytes and many polychromatophilic red corpuscles. A relatively large number of nucleated red corpuscles were seen, 80 per cent. of which were typical megaloblasts, the remainder being normoblasts. A differential count of the leucocytes showed the lymphocytes to be distinctly increased (26.5 per cent.). On October 6th the blood count was, reds 1,348,000, whites, 3000; haemoglobin 31 per cent. Up to this time the patient had had two courses of Fowler's solution, but the physiological limit of the dose had not been reached. On October 10th the extract of bone marrow was ordered, the blood count next morning being, reds 1,550,000, whites 3500; haemoglobin 35 per cent. The marrow was continued for two weeks, during which time the patient failed visibly, the red corpuscles sinking to 822,000; haemoglobin 18 per cent. On October 27 the extract was discontinued and Fowler's solution in increasing doses was ordered.

Stained specimens of the blood, taken on Oct. 27th, showed an interesting state of things. While the poikilocytosis, or deformity in shape and size of the red corpuscles, was markedly increased, the nucleated red corpuscles had almost entirely disappeared, only one megaloblast being seen in four specimens. Such a disappearance of the nucleated red corpuscles from the circulation may be interpreted in two ways: either the blood condition has improved to such an extent that great activity on the part of the blood-making organs is no longer necessary, or it has deteriorated so much that new formation is no longer possible. The latter condition obtained in a case of fatal purpura haemorrhagica reported by the writer in the *Johns Hopkins Hospital Bulletin*, May, 1894. Ehrlich

has also reported two cases. In the present case this was also the condition that probably prevailed. Blood count Nov. 3d, reds 900,000, whites 2000; haemoglobin 21 per cent. Stained specimens of the blood on Nov. 3d showed about the same condition of things as on Sept. 2d. The differential count of the leucocytes is so typical that it will be given in full :

Large				
Polynuclears.	Lymphocytes.	mononuclears.	Transition.	Eosinophiles.
52.1 per cent.	32.2 per cent.	2.4 per cent.	4.2 per cent.	6.1 per cent.

Nucleated red corpuscles again appeared in the blood in relatively large numbers, 59 being seen while making a differential count of 500 leucocytes.* This reappearance of the nucleated red corpuscles may be taken as a relatively favorable sign, showing that the blood-making organs are once more active. If improvement occurs in this case under the use of arsenic it will be slow, as it requires some time to safely increase the dose to the physiological limit (20 to 25 min. t. i. d.). The general record of the case is given in chart 2.†

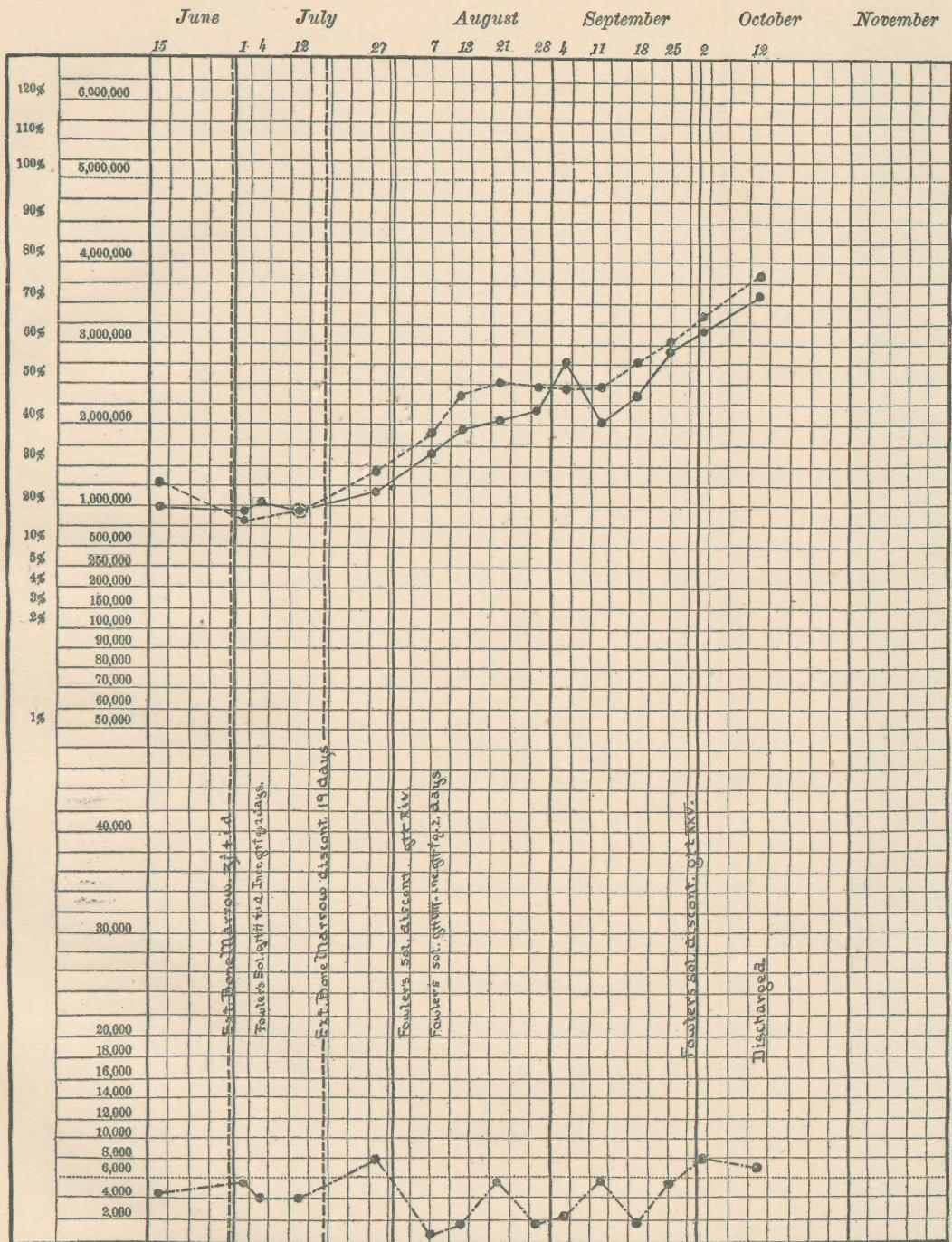
It will be seen that the two cases of chlorosis were benefited by the use of extract of bone marrow, while the two cases of pernicious anaemia were unimproved. It is difficult to understand how this remedy could be of service in cases of pernicious anaemia. Its effects can hardly be considered as analogous to those produced by thyroid extract in myxoedema. In the latter case there is atrophy of the gland, giving rise to defective secretion, so that there is an indication for attempting to supply this defect by the administration of thyroid extract. But the marrow in pernicious anaemia is, if anything, in a state of hypertrophy, and the condition is far more analogous to that of the hypertrophied and supposedly over-active thyroid gland in exophthalmic goitre than to that of the atrophied gland in myxoedema. Besides, there is no proof

* This is a very convenient mode of expressing the number of nucleated red corpuscles present in a specimen of blood, but we must always take into consideration the number of leucocytes per cmm. For example, suppose case A shows 2000 leucocytes per cmm., and case B 6000. Now while making a differential count of 500 leucocytes in a stained specimen from A we see 12 nucleated reds, in a similar count in a specimen from case B we see only 4 nucleated reds. Yet the number of nucleated red corpuscles in the blood is about equal in the two cases, as in case B we cover only one-third of the ground that we do in case A.

† Since the above went to press this patient has died. A final blood count on Nov. 16, made 24 hours before death, showed only 700,000 reds, 1000 whites; haemoglobin 17 per cent. No autopsy.

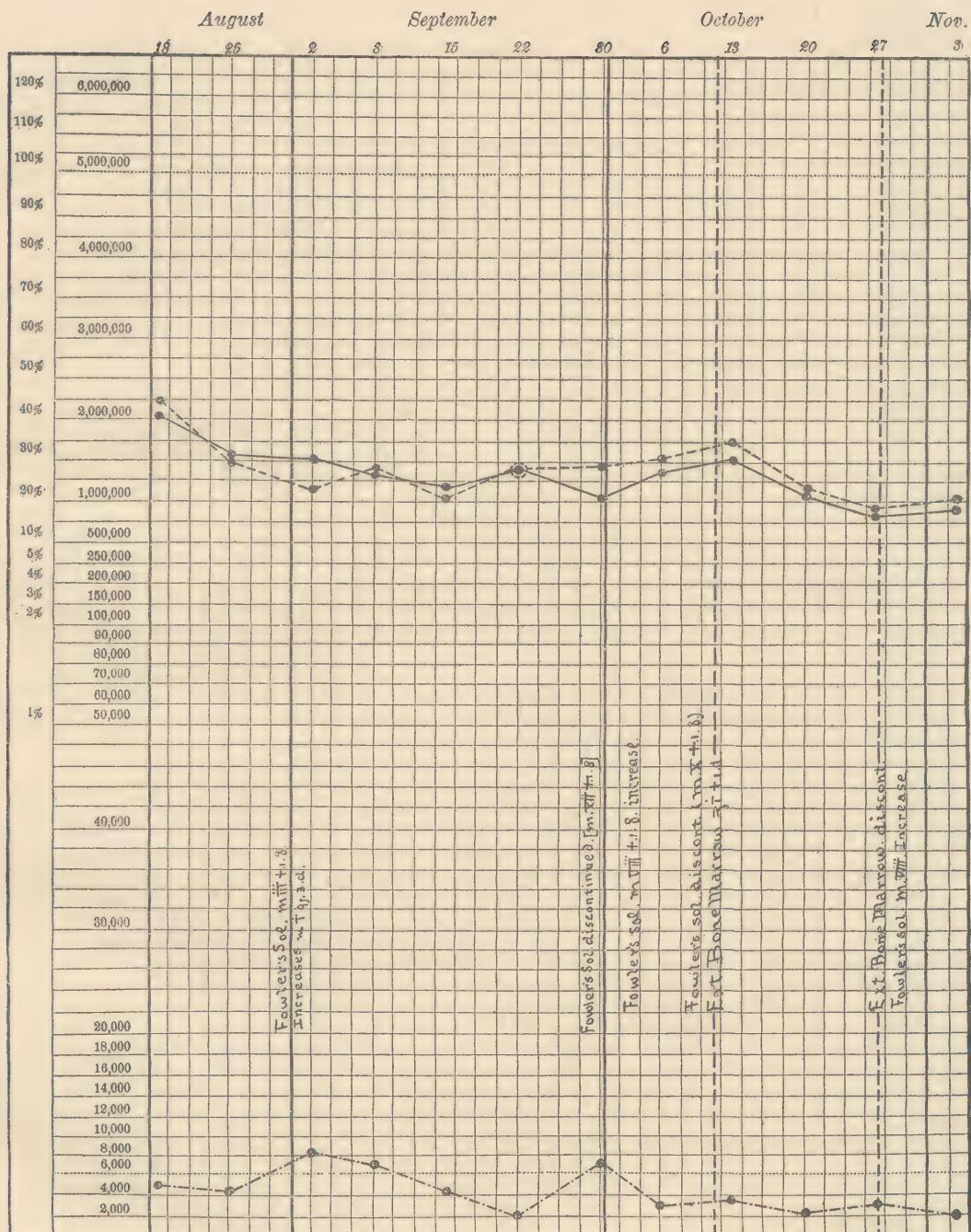
whatever that the marrow acts as a gland in the ordinary sense of the word. The formation of red blood corpuscles by the bone marrow cannot be properly termed a secretion, it being rather a process of cell multiplication and development, and there is no proof that this process is influenced in any way by any chemical product of the marrow itself. As regards the cases reported by previous observers, two things may be noted. First, there is room for doubt that they were true cases of pernicious anaemia. Second, the patients were given arsenic together with the bone marrow. Now it is well known that some cases of pernicious anaemia do remarkably well on arsenic, and several instances of apparent cure have been reported. Such an improvement is shown in Case 3 of our series.

It is different as regards the use of bone marrow in chlorosis. The marrow contains iron in considerable quantity, and we may reasonably suppose that the glycerin extract contains sufficient iron in organic combination to be of service in chlorosis, a disease which yields so readily to iron in almost any form. Whether its value in such cases is greater than that of the various forms of iron used in medicine is doubtful. This is well shown in chart 3, where a blood chart of a case of chlorosis treated with Blaud's pills is given together with that of Case 2 of our series. The former does not suffer by the comparison. The conclusion is that the extract of bone marrow may be of value in cases of ordinary anaemia and chlorosis, such as would be benefited by iron in other forms, but that there is no proof of its being of value in cases of primary pernicious anaemia.



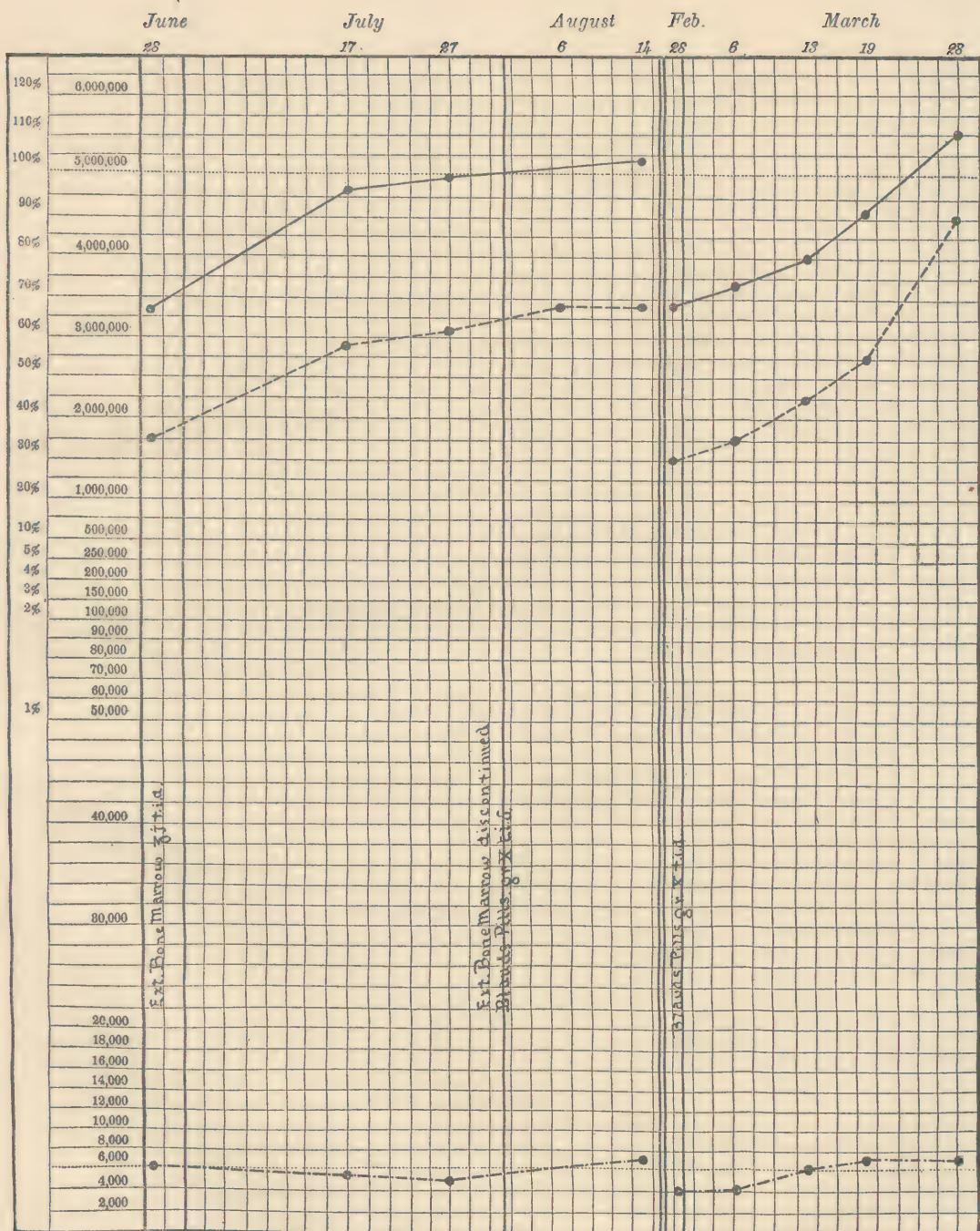
Black = red corpuscles. Broken = hæmoglobin. - - - = colorless corpuscles.

No. 1. J. K. PERNICIOUS ANÆMIA. CASE 3.



Black = red corpuscles. Broken = haemoglobin. - - - = colorless corpuscles.

No. 2. J. R. PERNICIOUS ANÆMIA. CASE 4.



Black = red corpuscles. Broken = haemoglobin. ---- colorless corpuscles.

No. 3. J. H. CHLORO-ANÆMIA. CASE 2. E. S. CHLOROSIS.

